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An Efficient, Rapid and Highly Selective Preparation of the Wieland-Miescher Ketone-9-Ethylene Ketal

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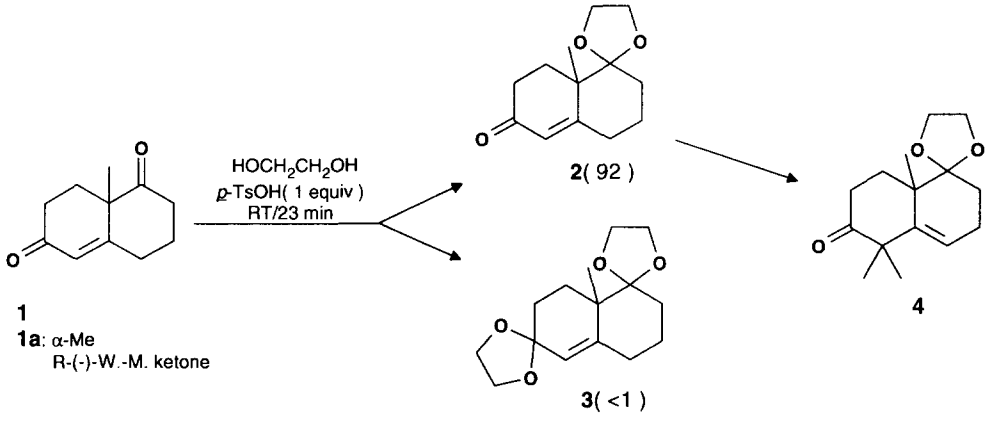
Abstract: Reaction of the Wieland-Miescher ketone **1** in ethylene glycol at room temperature using **one equivalent** of *p*-toluenesulphonic acid gives the 9-ethylene ketal **2** in ≥90% yield and 92% selectivity.

The Wieland-Miescher Ketone **1**[2] has served as starting material in many syntheses of Natural Products. The most common first step in such efforts is the selective protection of the C9-ketone as the ethylene ketal **2** to allow subsequent manipulations at the enone unit without interferance from the saturated ketone.



The classical ketalization of **1** ($HOCH_2CH_2OH$/PhH/*p*-TsOH/reflux),[3] apart from utilizing benzene as solvent,[4] was capricious in our hands often resulting in moderate yields (*cf* ref. 3a) due to varying amounts of unchanged diketone **1** and bisketal **3** as byproducts, especially when carried out on a large scale.[5] Although the monoketal **2** can be crystallized preferentially from the product mixture, one has to invariably resort to chromatography of the mother liquors in order to extract all of this valuable material. The more byproducts, (**1** and **3**) the crude product mixture contains, the less efficient is the preferential crystallization of **2**. The thus unavoidable chromatography is very tedious, since monoketal **2** is the middle one of three very closely running components (**1**, **2** and **3**) on silica gel and can be difficult to separate cleanly unless an appropriately large amount of silica gel is used.[6] Although for many purposes such as deconjugative enone-dimethylation (**2** --->

4)[7] the presence of small amounts of **3** (containing no enolizable protons) is of no consequence,[5] the same does not apply to unchanged diketone **1** in the product mixture. To avoid this, the ketalization reaction can be driven in order to consume all the diketone, but one pays for this with a larger amount of bisketal side product.[5] An alternative ketalization method[8] relies upon the transketalization from butanone ethyleneketal to **1** at room temperature, however with very long reaction times especially if one wants to ensure the complete consumption of starting material.[5] Finally monoketalization can be achieved, albeit in only 73% by using 1,2-*bis*-trimethylsilyloxyethane in dichloromethane at -78°C - -10°C/8.5 h. with trimethylsilyltriflate as catalyst.[9]

In summary a quick, reliable and reproducible preparation of the monoketal **2** with as little **1** and **3** side products as possible and which a) routinely provides the majority of the product via preferential crystallization and b) keeps chromatography to a minimum is required.

We report here a remarkably fast method for the selective C9 ketalization of **1** with negligible loss of material as the bisketal **3**. Namely by allowing the diketone to react with ethylene glycol as solvent in the presence of a **stoichiometric amount** of *p*-toluenesulphonic acid we were able to reproducibly obtain high yields of **2** in less than 30 min at room temperature.[10] The **only appreciable side product** is unchanged Wieland-Miescher ketone **1**, which can be recycled. NMR spectra indicated, that the crude product mixture contained: monoketal (92%), Wieland-Miescher ketone (7%) and bisketal (<1%).[11] In experiments carried out on milligramm- up to 26 g scales we routinely were able to isolate pure monoketal **2** in ≥ 90%. We believe this to be the method of choice for the preparation of this important synthetic intermediate.

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10. **Procedure:** The Wieland-Miescher ketone **1** (26 g, 146 mmol) was dissolved in ethylene glycol (730 ml) containing 4Å molecular sieves. *p*-TsOH (27.8 g, 1 eq) was added all at once, and the resulting solution was stirred at room temperature for 23 min, after which it was poured carefully into a mixture of ice and sat. aqueous $NaHCO_3$. The solution was then extracted with EtOAc (4x), the organic phases washed with brine and the brine layer back-extracted with EtOAc. Finally the combined organic extracts were dried (Na_2SO_4), filtered and concentrated to a pale yellow oil, crystallization of which from *i*-Pr_2O gave the desired monoketal **2** in two crops (14 g & 10 g). Flash chromatography of the mother liquor (eluent - EtOAc:cyclohexane; 2:1) provided more of **2** (4.5 g) and crystallization of mixed fractions resulted in a final crop (0.5 g); total yield: (29 g, 89.5%). An identical procedure employing optically active R-(-)-Wieland-Miescher ketone **1a** (α_D^{25} -99°, *c* 1.07, toluene) provided R-(-)-**2** in 90% (α_D^{25} -129°, *c* 1.1, toluene), m.p. 51 - 52°C (*i*-Pr_2O).
11. **The bisketal was very slow in forming!** In a control experiment, even after 1 hour we observed an unchanged ratio of **1**:**2**:**3**. Overnight other products appeared, but crude NMR analysis still indicated >80% monoketal **2** in the product mixture with < 5% of each of **1** and **3**.

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